REMARKS

Applicants note the acknowledgement of the election without traverse of Group III, claims 53-58, and the withdrawal of claims 1-52 and 59-65, pursuant to 37 C.F.R. § 1.142(b).

Claims 1-52 and 59-65 are cancelled without prejudice. Claims 66-79 have been newly added. Claims 53-58 and 66-79 are pending in the above-identified application. Claims 53-58 stand rejected under 35 U.S.C. § 103(a).

I. Amendment to the Specification

In accordance with the Examiner's request (Office Action, page 2, section 3), the title of the invention has been changed to be more clearly indicative of the invention to which the claims are directed. Support for this amendment can be found through the application as filed and specifically at page 11, lines 1-4; page 22, lines 14-22 and page 23, lines 1-5; and page 46, claim 53.

II. Amendment to the Claims

Claims 1-52 and 59-65, which were previously withdrawn, are currently cancelled without prejudice. Claim 53 has been amended. Claims 66-79 have been newly added. Support for the amendments can be found throughout the application and particularly at page 14, lines 6-20; page 17, lines 3-11; page 18, lines 7-17; page 22, lines 4-22 to page 23, lines 1-22 continuing to page 24, lines 1-5; page 24, lines 20-22 to page 25, lines 1-5; and page 33, lines 5-20. It is submitted that no new matter has been added.

III. Clarification of Ownership

The Examiner requested clarification regarding the ownership of the claimed invention to consider patentability of the claims under 35 U.S.C. § 103(a) (Office Action, page 3, section 4). Applicants believe that the current inventorship of claims 53-58 and 66-79 is proper.

IV. Rejection of the claims under 35 U.S.C. § 103(a)

(a) Claims 53-56 and 58 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Nycz et al. (*Analytical Biochemistry*, **259**:226-234, 1998).

Specifically, the Examiner argues that "one of ordinary skill in the art would have been motivated to combine of [*sic*] reverse transcriptase and single stranded binding protein because with the inclusion of the single-strand binding protein, the amplification efficiency increases (Nycz et al., p.226, column 1, Abstract)." (Office Action, page 4, section 5). The Examiner further alleges that "one of ordinary skill would have also varied the reaction condition by optimizing the concentration of the single-strand binding protein and the temperature of the reaction in order to optimize the reaction condition to maximize the amount of transcription product as it was routine procedure to optimize reagent condition in assays." (Office Action, page 4, section 5). Thus, the Examiner concludes that it would have been *prima facie* obvious to carry out the method as claimed. Applicants respectfully disagree and traverse the rejection.

To make a *prima facie* case of obviousness, the Examiner has the burden of showing either that some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art would lead that individual to arrive at the relevant teachings of the references. Indeed, the prior art must suggest the combination or convey to those of ordinary skill in the art a reasonable expectation of success of making it. Moreover, when evaluating a claim for determining obviousness, all limitations of the claim must be evaluated.

The Nycz et al. references teaches the procedure for amplification of an RNA target sequence comprising the steps of (a) reverse transcription to ***synthesize*** the target sequence (i.e. cDNA synthesis), followed by (b) strand displacement ***amplification***.

> "Two sequential steps are involved - target generation followed by exponential amplification. Target generation produces an amplifiable target with defined ends flanked by nickable restriction sites. This defined target is then exponentially amplified by repeated nicking, strand displacement, and primer hybridization. Figure 1 oulines the general procedure for amplification of an RNA target sequence (RT-SDA) using a reverse transcriptase to perform the first step of target generation (cDNA synthesis).
> The present report describes quantitative RT-SDA (QRT-SDA) using a control sequence for competitive amplification. In addition, we included a single-strand binding protein to improve amplification efficiency."

See Nycz et al. p.226, right column, second and third paragraphs.

According to Nycz et al., "amplification" occurs after reverse transcription has synthesized the target to be amplified. The process of ***reverse transcription is not amplification***; rather, amplification, as that term is used by Nycz and is commonly understood in the art, refers

to the step following reverse transcription when the synthesized cDNA is multiplied in a specific manner. Thus, when Nycz et al. alleges that T4gp32 improves "amplification efficiency," they are suggesting that the single-strand binding protein improves the post-reverse transcription step of amplification.

Significantly, although Nycz et al. discloses introduction of a single-strand binding protein for the purpose of enhancing amplification efficiency; there is no teaching or explanation of the basis for the alleged improvement in "amplification efficiency." Nycz et al. do not define anywhere in their article what they mean by the term "amplification efficiency" and no guidance is provided as to what the single-strand binding protein does to enhance amplification efficiency or what, in fact, is the measure of improved amplification efficiency. Thus it is not possible for one of ordinary skill in the art to conclude (other than said assertion of Nycz et al.) that inclusion of a single-strand binding protein is desirable in an amplification process, let alone, in a reverse transcription process. There is simply no teaching or suggestion that inclusion of a single-strand binding protein in a reverse transcription process would serve the purpose of promoting the completed reverse transcription of mRNA as is recited in claim 53. Certainly, absent any explanation for Nycz's assertion of improved amplification efficiency, there is no basis for one of ordinary skill in the art to expect any improvement in the processivity of reverse transcriptase upon inclusion of a single-strand binding protein.

Furthermore, Nycz et al. amplify targets with prescribed 5' and 3' primers, which makes it possible to amplify only the sequence of targets whose sequences are known. Applicants' invention is directed to synthesizing cDNA's from ***any*** mRNA molecules regardless of whether its sequence is known or unknown. In addition, Nycz's method generates products of ***at most*** 100 nucleotides, whereas Applicants' invention is directed to synthesizing completed cDNA's from mRNA molecules that are ***greater than*** 600 nucleotides long. Since there is no appreciation of the role single-strand binding protein plays in improving completed reverse transcription of mRNA, there is no motivation to use it in procedures involving longer targets.

The claimed invention is not directed to amplification; instead, it is directed to a method for ***synthesizing*** cDNA molecules, using "reverse transcriptase and a single-strand binding protein at a concentration sufficient to promote completed reverse transcription of mRNA molecules greater than 600 nucleotides in length." In summary, Nycz et al. makes use of single-

strand binding protein for an entirely different purpose (amplification) than in Applicants' invention (completed reverse transcription) using targets that fall outside the ranges recited in the claims and furthermore, provides no teaching or motivation to one of ordinary skill in the art to make Applicants' claimed invention.

Taken together, Applicants respectfully assert that the Nycz et al. reference has been improperly applied against Applicants' invention because the reference lacks the necessary teaching or suggestion of a method for synthesizing cDNA molecules, using "reverse transcriptase and a single-strand binding protein at a concentration sufficient to promote completed reverse transcription of mRNA molecules greater than 600 nucleotides in length." The alleged improvement in amplification efficiency on small (<100bp) targets provides no motivation to use a single-strand binding protein in a different process (synthesis) or on targets longer than 600 base pairs. Furthermore, there is no expectation, based upon the teachings of the prior art, that the combination of a reverse transcriptase and single-strand binding protein in cDNA formation leads to completed synthesis of target mRNA's longer than 600 base pairs. Thus, Applicants request that this rejection be withdrawn.

(b) Claim 57 stands rejected under 35 U.S.C. § 103(a) as purportedly being obvious over Nycz et al. (*Analytical Biochemistry*, **259**:226-234, 1998) in view of Cleuziat et al. (US Patent No. 5,849,547).

For the reasons detailed above, the primary reference, Nycz et al. provides no teaching or motivation to arrive at Applicants' invention. This deficiency is not remedied by the secondary reference, Cleuziat et al.

Cleuziat et al. describe a method of amplifying a target nucleic acid sequence (RNA and/or DNA) by transcription reaction using displacement. It discloses the possibility of using reverse transcriptase to make cDNA and single strand binding protein from *E.coli* for strand displacement. However, this reference does not provide any motivation or teaching to combine reverse transcriptase and single strand binding protein to synthesize full-length cDNA from mRNA molecules. Furthermore, there is no basis in Cleuziat et al. to combine it with Nycz et al.

Because the secondary reference fails to teach or suggest a method of synthesizing full-length cDNA molecules, the combined references do not render the claimed invention obvious.

For the foregoing reasons, the claims are not obvious over Nycz et al. Therefore, it is respectfully requested that this rejection be withdrawn.

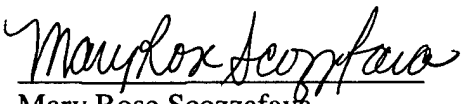
V. Conclusion

In view of the amendment and arguments made above, Applicants conclude that the outstanding rejections of record have been overcome. The present invention is, thus, now believed to be in condition for allowance.

No fees are believed to be due; however, the Office is authorized to charge any fees to our Deposit Account No. 08-0219. Should the Examiner consider that a discussion would be helpful in moving the application to allowance, the Examiner is requested to contact the undersigned at the address below.

Respectfully submitted,

Date: May 12, 2003



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